II. RESPONSE

A. Status of the Claims

Claims 67-69, 73, and 98-103 were pending at the time of the Action. Claims 69, 98-99, and 103 have been canceled. New claims 104-107 have been added. Thus, claims 67-68, 73, 100-102, and 104-107 are now pending. Support for new claim 104 can be found in the specification in the sentence bridging pages 7 and 8, and in the first paragraph on page 1. Support for new claims 105-107 can be found at, for example, page 3, lines 10-25.

B. Objection to the Figures

The Action objects to FIGs. 10a, 10b, and 11 because they contain sequences that are duplicative of sequences provided in the sequence listings. Applicant notes, however, that the present application was filed under 35 U.S.C. § 371. With regard to such application, 37 C.F.R. § 1.83(a) states that "tables and sequence listing that are included in the specification are, except for applications filed under 35 U.S.C. § 371, not permitted to be included in the drawings." Accordingly, FIGs. 10a, 10b, and 11 are in compliance with the Patent Rules. Applicant, therefore, respectfully requests the withdrawal of this objection.

C. Objection to the Specification

The specification was objected to because it contained an embedded hyperlink at page 14, lines 17-18. The specification has been amended to remove the embedded hyperlink. Applicant, therefore, respectfully requests the withdrawal of this objection.

D. The Claims are Enabled

The Action rejects claims 67-69, 73, and 98-103 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicant traverses this rejection.

As noted in the Action, the factors to be considered when determining whether a disclosure satisfies the enablement requirement include: (1) the breadth of the claims; (2) the

nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d at 737, 740.

The Action points to the following factors in support of its rejection: the breadth of the claims; the lack of guidance in the specification; the lack of working examples; and the unpredictability of gene/protein therapy. Applicant addresses each of these points below.

1. The Breadth of the Claims

Current claim 67 is directed to a method of treating an ACE2 decreased state comprising administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, a therapeutically effective amount of an ACE2 polypeptide.

2. The Guidance Provided by the Specification

The Action asserts that the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any mammal; and (ii) how the claimed method would have resulted in providing ACE2 to cells in an amount sufficient to treat an ACE2 decreased state (Action, p. 6). The present specification provides sufficient guidance in these areas for at least the following reasons.

The present specification provides a new paradigm for the regulation of the renin-angiotensin system. The present specification discloses that hypertension, as well as other cardiac, lung, and kidney diseases are associated with an ACE2 decreased state (*see e.g.*, p. 2, ln.

28 to p. 3, ln. 6). In particular, the rat and mouse studies in the present specification demonstrate that an ACE2 decreased state is associated with cardiovascular, renal, and lung diseases. For example, decreased ACE2 mRNA and protein levels were observed in the kidneys of hypertensive rats (Specification, p. 32, ln. 21 – p. 33, ln. 22). In studies on the ACE2 knockout mouse, it was observed that loss of ACE 2 leads to detrimental effects in the kidneys (p. 36, ln. 8-11), heart defects (p. 36, ln. 14 – p. 38, ln. 12), and increases the susceptibility of the lungs to injury (p. 40, ln. 12-20). Accordingly, those of ordinary skilled in the art would have appreciated the therapeutic benefit of a method of treating an ACE2 decreased state comprising administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, a therapeutically effective amount of an ACE2 polypeptide.

Enablement must be assessed from the position of a person of ordinary skill in the art. Acton *et al.* (US 6,194,556), which is cited in present specification (p. 2, ln. 11) and in the Action, shows that ACE2 was fully available to those in the art at the time the present application was filed as a nucleotide sequence, as well as in vectors and plasmids for ACE2 expression (*e.g.* '556 patent, column 29, lines 15 to column 30 line 52). Polypeptides of ACE2 are disclosed in the '556 patent from column 30 to column 37 line 26. In addition, pharmaceutical preparations and formulations of ACE2 are disclosed in the '556 patent at column 61 line 37 to column 36 line 37. The present specification on page 18, third paragraph, even sites to the '556 patent's corresponding Canadian patent CA 2,372,387 as describing methods by which ACE2 may be produced. A further document cited in the present specification on page 18, third paragraph, is Nichols *et al.* (JBC 277 (17):14838-14843 (2002)). Nichols shows an assay for ACE2 activation based on its proteolytic activity on small peptides. Thus, those of ordinary skill in the art would

have been able to make and use ACE2 polypeptides without undue experimentation in view of the teachings in the specification and the knowledge in the art.

The previously provided reference by Imai *et al.* (*Nature*, 436:112-116 (2005); IDS reference C61)) is further evidence that those of skill in the art can make and use the claimed invention without undue experimentation (*see* Neu Declaration, para. 7). Imai *et al.* demonstrated that injecting ACE2 knockout mice or acid-treated wild-type mice with a recombinant human ACE2 protein protected the mice from severe acute lung injury (p. 112, col. 2; Figures 2(d)-(f)). This study employed the same ACE2 knockout mouse model described in the present specification, the same lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) disclosed in the specification (*see* p. 21, ln. 27-30). Thus, Imai *et al.* demonstrate that those of skill in the art can practice a method of treating an ACE2 decreased state comprising administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, a therapeutically effective amount of an ACE2 polypeptide. The results of Imai *et al.* also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was able to complement ACE2 function in mice (Neu Declaration, para. 7).

In another study described in the declaration of Dr. Nikolaus Neu ("the Neu Declaration"), recombinant human soluble ACE2 (rhACE2) protein was studied in a piglet acute respiratory distress syndrome (ARDS) model (Neu Declaration, para. 8). The study was conducted by Alexander Löckinger and Benedikt Treml of Dr. Neu's research group, with the pharmacological evaluation being carried out by Manfred Schuster and Hans Loibner of Apeiron (Neu Declaration, para. 8). Aperion is the licensee of the present patent application. In this

study, an ACE2 polypeptide, rhACE2, was administered as a central venous bolus injection at a dose of 100 μg/kg following the last LPS bolus injection and 120 minutes from the start of the continuous LPS infusion (Neu Declaration, para. 9). Intravenous injection is a route of administration disclosed in the present specification (*see* Specification, p. 21, ln. 27-30; Neu Declaration, para. 9). The rhACE2 bolus injections were well tolerated and did not show any apparent side effects (Neu Declaration, para. 9). Treatment with rhACE2 stabilized or even decreased slightly pulmonary arterial pressure (PAP), while the control group showed a nearly 15% increase in PAP (Neu Declaration, para. 11). Systolic arterial pressure (SAP) was also measured. The control group showed an increase in SAP up to 12%, whereas after rhACE2 injection a stabilization and 5% decrease in SAP was observed (Neu Declaration, para. 11). The difference between the control and rhACE2 treatment groups was significant (Neu Declaration, para. 11).

In addition, oxygen concentration was measured in arterial and venous blood samples taken from the piglets every 30 minutes (Neu Declaration, para. 12). There was a potential stabilization observed of arterial as well as venous oxygen concentration in the group receiving rhACE2, however the data did not reach statistical significance in this study and will have to be confirmed in further experiments (Neu Declaration, para. 12). The results of this study also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was used to treat pigs.

The evolutionary conservation of ACE2 structure and activity among mammals, as well as other organisms, is further evidence that the currently claimed method could be practiced in any mammal (*see e.g.,* Specification, FIGs. 1A, showing an alignment of the amino acid sequences of ACE2 from human, rat, and mouse, which illustrates the identities and similarities

between these sequences). In addition, results in flies showed that a P-element mutation associated with the ACE homologue, ACER, results in a severe and lethal defect of heart morphogenesis providing further evidence that ACE/ACE2 functions in the heart have been conserved through evolution (Specification, p. 30, ln. 28 to p. 31, ln. 2). In Applicant's previous response, Applicant also provided a publication entitled "Structure, Evolutionary Conservation, and Function of Angiotensin- and Endothelin-Converting Enzymes" (Macours *et al.*, *International Review of Cytology*, 239:47-97 (2004)), as further evidence of the conservation of the ACE/ACE2 system.

Furthermore, the specification discloses that AngI and AngII are substrates for ACE2, which functions as a carboxypeptidase to cleave a single residue from each of AngI and AngII (p. 2, ln. 5-10). Applicant also provided previously the results of a BLAST search of the ACE2 substrate, AngII, which shows that AngII is present in numerous mammals including *Pan troglodytes, Mus musculus, Homo sapiens, Callithrix jacchus, Gorilla gorilla, Canis familiearis, Macaca mulatta, Rattus norvegicus, Ovis ammon,* and *Pongo pygmaeus*. In view of the evidence that ACE2 structure and function is conserved among mammals, one would expect that the currently claimed method could be practiced in any mammal (*see* Neu Declaration, para. 5).

In view of the *in vivo* rat and mouse data on the role of ACE2 in cardiac, lung, and kidney diseases; the disclosed similarities of the rat, mouse, and human ACE2 sequences; and the knowledge in the art of ACE2 sequences, expression constructs, and formulations; those of ordinary skill in the art could have practiced the claimed method in a multitude of mammals including humans. This is confirmed by the studies described in Imai *et al.* and in the Neu Declaration.

3. The Existence of Working Examples

The Action states that the working examples in the specification demonstrate the role of ACE2, but do not disclose any method of treating any condition by administering any composition of ACE2. Applicant notes, however, that a specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. MPEP § 2164.02. As described in the preceding section, Imai *et al.* demonstrated that one skilled in the art is be able to practice the claimed invention without an undue amount of experimentation by demonstrating that a recombinant human ACE2 protein protected mice having a decreased ACE2 state from severe acute lung injury (p. 112, col. 2; Figures 2(d)-(f)) in a study that employed the same ACE2 knockout mouse model described in the present specification, the same lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) disclosed in the specification (*see* p. 21, ln. 27-30) (*see also* Neu Declaration, para. 7). The enablement of the currently claimed invention is further confirmed by the study in the piglet ARDS model discussed above and described in the Neu Declaration (para. 8-12).

4. The Unpredictability of Gene/Protein Therapy

The Action asserts that gene therapy and protein therapy are unpredictable (Action, p. 6). However, it appears that all of the Action's arguments and evidence of unpredictability pertain to gene therapy or to safety and efficacy issues (*see* Action, p. 7-19). As an initial point, the current claims are directed to administering an ACE2 polypeptide; thus, the Action's arguments regarding gene therapy are moot.

In regard to administering polypeptides, the Action points to references teaching the importance of dosing, clearance and efficacy of the product, preclinical evaluation for toxicity and immunogenicty (Action, p. 17). The MPEP states, however, that an applicant need not

demonstrate that the invention is completely safe (MPEP § 2164.01(c)). Furthermore, testing for the full safety and effectiveness of a particular drug for human use is more properly left to the Food and Drug Administration (FDA). *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *Id.* The stage at which an invention in the pharmaceutical field becomes useful is well before it is ready to be administered to humans. *Id.*

Moreover, there is nothing in the patent statute or any other statutes that gives the Patent Office the right or the duty to require an applicant to prove that compounds he is claiming, and which he has stated are useful for "pharmaceutical applications," are safe, effective, and reliable for use with humans. *In re Krimmel*, 292 F.2d 948, 954 (C.C.P.A. 1961); *see also* MPEP § 2164.01(c).

The Examiner has the initial burden of producing reasons that substantiate a rejection based on lack of enablement. The Action's generalizations about clinical safety and efficacy fail to satisfy this burden. Furthermore, even if the Action had shifted the burden on enablement, the Action's allegations of unpredictability and undue experimentation are rebutted by the showing that a recombinant human ACE2 protein protected mice having a decreased ACE2 state from severe acute lung injury (Imai *et al.*, p. 112, col. 2; Figures 2(d)-(f)) in a study that employed the same ACE2 knockout mouse model described in the present specification, the same lung elastance assay described in the specification (*see* p. 40, ln. 12-20), and a route of administration (intraperitoneal injection) disclosed in the specification (*see* p. 21, ln. 27-30). The Action's allegations of unpredictability and undue experimentation are also rebutted by the showing that the administration of an ACE2 polypeptide in a porcine lung disease model resulted in the

stabilization and even decrease in both pulmonary arterial pressure and systolic arterial pressure (*see* Neu Declaration, para. 11).

Moreover, the use of protein therapy in the treatment of diseases is well-known in the medical field (Neu Declaration, para. 6). Examples of such protein therapies are described in the publication *Scientific Considerations Related to Developing Follow-On Protein Products*, 2004, which is cited in the Action. This publication mentions such drugs as Epogen®, which is a protein therapy based on human erythropoietin; and Neupogen®, which is a protein therapy based on granulocyte colony-stimulating factor (*see,* p. 1, 2nd para.). As pointed out in the Action, *Scientific Considerations Related to Developing Follow-On Protein Products* also notes that six companies manufacture FDA-approved versions of human growth hormone (paragraph bridging pages 5-6). "Since ACE2 is an endogenous protein in mammals and the present specification discloses the physiological role of ACE2, it would require only routine clinical studies to administer a therapeutically effective amount of an ACE2 polypeptide to an mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, in order to treat the mammal as recited in the current claims." (Neu Declaration, para. 6).

5. Summary

In view of the rat and mouse animal model studies in the specification showing the role of ACE2 in cardiac, lung, and kidney diseases; the disclosed similarities of the rat, mouse, and human ACE2 structure and function; and the teaching in the specification that an ACE2 decreased state, such as cardiac, lung, and kidney disease, may be treated by administering to an animal in need thereof an effective amount of an agent that can increase the expression of ACE2; a person of ordinary skill in the art could make and use the currently claimed invention without undue experimentation (*see* Neu Declaration, para. 14). The enablement of the claims is

confirmed by the demonstration by Imai *et al.* that injecting ACE2 knockout mice or acid-treated wild-type mice with a rhACE2 protein protected the mice from severe acute lung injury; and the study in the piglet ARDS model showing that rhACE2 protein therapy stabilized or even decreased both pulmonary arterial pressure and systolic arterial pressure (*see* Neu Declaration, para. 14).

The current claims are, therefore, enabled. Thus, Applicant respectfully requests the withdrawal of this rejection.

E. The Claims Satisfy the Written Description Requirement

The Action rejects claims 67-69, 73, and 98-103 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Action acknowledges that the specification describes the complete structure of mouse, rat, and human ACE2, and that the specification identifies the zinc binding site, the catalytic center, the signal peptide, and the transmembrane domain of ACE2 (Action, p. 21). In addition, the Action acknowledges that the specification describes the function of ACE2 (Action, p. 8-9). Nevertheless, the Action asserts that there is an absence of sufficient recitation of the distinguishing identifying characteristics of the genus of ACE2 fragments and compounds encompassed by the claims (Action, p. 22). Applicant traverses this rejection.

In rejecting a claim under the written description requirement, the Action is required: (1) to set forth the claim limitation not described; and (2) to provide reasons why a person skilled in the art would not have recognized the description of the limitation in view of the disclosure of the application as filed. *Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, Paragraph 1.* It appears, however, that in making the present written description rejection, the Examiner did not apply the proper legal standard.

The written description requirement for a claimed genus may be satisfied through sufficient description of a **representative number** of species. It is not necessary that every permutation within a generally operable invention be effective for Applicant to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). The current claims are directed to administering an ACE2 polypeptide. The Action acknowledges that the specification describes the complete structure of ACE2 from three different mammalian species (rat, mouse, and human). The specification also acknowledges that the specification identifies the zinc binding site, the catalytic center, the signal peptide, and the transmembrane domain of ACE2 (Action, p. 21). In addition, the Action acknowledges that the specification describes the function of ACE2 (Action, p. 8-9). Thus, in view of the disclosure of three mammalian ACE2 sequences, the evolutionary conservation of ACE2 structure and activity, ACE2 function, and a correlation between ACE2 structure and function, a person of ordinary skill in the art can reasonably concluded that Applicant had possession of a representative number of ACE2 polypeptides at the time of filing (*see also* Neu Declaration, para. 13).

As described in Applicant's previous response, FIG. 1A in the present specification provides an alignment of the amino acid sequences of ACE2 from human, rat, and mouse, which illustrates the identities and similarities between these sequences. In addition, results in flies showed that a P-element mutation associated with the ACE homologue, ACER, results in a severe and lethal defect of heart morphogenesis providing further evidence that ACE/ACE2 functions in the heart have been conserved through evolution (Specification, p. 30, ln. 28 to p. 31, ln. 2). As further evidence of the conservation of the ACE/ACE2 system, Applicant previously provided a publication entitled "Structure, Evolutionary Conservation, and Function

of Angiotensin- and Endothelin-Converting Enzymes" (Macours *et al.*, *International Review of Cytology*, 239:47-97 (2004)). In addition, the enclosed BLAST search of the ACE2 substrate, AngII, shows that AngII is present in numerous mammals including *Pan troglodytes, Mus musculus, Homo sapiens, Callithrix jacchus, Gorilla gorilla, Canis familiearis, Macaca mulatta, Rattus norvegicus, Ovis ammon,* and *Pongo pygmaeus*.

FIG. 1B is a schematic representation of ACE and ACE2 in which (1) the zinc binding site, (2) the catalytic center, (3) the signal peptide, and (4) the transmembrane domain are identified. Furthermore, the specification discloses that AngI and AngII are substrates for ACE2, which functions as a carboxypeptidase to cleave a single residue from each of AngI and AngII (p. 2, ln. 5-10). The specification also discloses the expression pattern of ACE2 (p. 2, ln. 3-5) and that ACE2 inhibitors are known in the art (p. 2, ln. 15-17). Thus, the present specification discloses: (1) ACE2 structure; (2) ACE2 function; (3) a known correlation between ACE2 structure and function; and (4) that ACE2 has been conserved through evolution. Applicant further notes that the structure of human ACE2 was also provided in the Acton patents (U.S. Patents 6,194,556 and 6,632,830) cited in the Action (*see e.g.*, '556 patent, col. 3, ln. 4-43; '830 patent, col. 4, ln. 46 to col. 5, ln. 38).

Imai *et al.* (*Nature*, 436:112-116 (2005); IDS reference C61) is further evidence that the present specification's disclosed *in vivo* role of ACE2 in the regulation of the renin-angiotensin system is correct and would have been understood by a person of ordinary skill in the art. Kuba *et al.* (*Nature Medicine*, 11:875-879 (2005); IDS reference C62) is further evidence that lung injury is an ACE2 decreased state (*see e.g.*, p. 875, col. 2, second paragraph). Imai *et al.* reported that ACE2 protected mice from severe acute lung injury, whereas other renin-angiotensin components such as ACE and AngII induced lung edemas and impaired lung repair

(*see* Abstract). As shown in Figures 2(d)-(f) of Imai *et al.*, treatment of ACE2 knock-out mice with a recombinant human ACE2 protein, an ACE2 activator, resulted in the attenuation of lung injury. These results provide further support that ACE2 functions as a negative regulator of the renin-angiotensin system and, therefore, that an ACE2 activator should be used to treat an ACE2 decreased state such as lung injury. The results of Imai *et al.* also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was able to complement ACE2 function in ACE2 knock-out mice. The Research Report described in the Neu Declaration showed that the administration of a recombinant human ACE2 protein in a porcine lung disease model resulted in the stabilization and even decrease in both pulmonary arterial pressure and systolic arterial pressure (*see* Neu Declaration, para. 11); thus providing further evidence of the conserved function of ACE2 and the renin-angiotensin system.

In view of the above, the present specification describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that Applicant had possession of the claimed invention at the time of filing. This is further supported by the Neu Declaration, which stated that the description in the specification showed that "at the time the application was filed the inventors of the present application were in possession of a method of treating an ACE2 decreased state comprising administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease, a therapeutically effective amount of an ACE2 polypeptide." (Neu Declaration, para. 13). Applicant, therefore, requests the withdrawal of this rejection.

F. The Claims Are Novel Over the Cited Art

1. U.S. Patent 6,194,556

The Action rejects claims 67-68 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 6,194,556 (the '556 patent). Applicant traverses this rejection.

In response to Applicant's previous argument, the Action states that "the recitation of Ace2 decrease [sic] state has not been given patentable weight because the recitation occurs only in the preamble." (Action, p. 26). This assertion is incorrect. At the time of the Action, claim 67 recited, in the body of the claim, "administering to a mammal having ***an ACE2 decreased state***...." Furthermore, current claim 67 now incorporates the limitations of claim 69, which was not rejected as being anticipated, in reciting "administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease...." Thus, the Action's only grounds for maintaining the present anticipation rejection are not valid. Applicant, therefore, respectfully requests that the rejection be withdrawn.

G. Conclusion

In view of the above, Applicants believe that they have submitted a complete reply to the Office Action dated October 20, 2006. Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicant's representative at (512) 536-5654.

Respectfully submitted,

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